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(54) Title: BIODEGRADABLE POROUS SCAFFOLD MATERIAL

(57) Abstract: The invention relates to a method for the preparation of a porousbody of a biodegradable material comprising the steps of mixing a copolymer of polyakylene glycol terephtalate and an aromatic polyester with particles that are soluble in a solvent in which the copolymer essentially does not dissolve, and subjecting the obtained mixture to heat and/or pressure sufficiently long for forming the body. The invention further relates to a porous body obtainable by said method and to its use as a scaffold for tissue engineering or as a medical implant.

Title: Biodegradable porous scaffold material

The present invention is directed to a method for the preparation of a porous body containing a biodegradable material, a porous body obtainable by said method, a medical implant or scaffold comprising said porous body and the use of said porous body in tissue engineering.

The application of porous implants in for instance reconstructive surgery or more in general in tissue (re)constructive engineering is well known. The application of various biodegradable polymeric materials has proven to be a very promising tool in tissue engineering. However, a demand remains for a wide variety of materials in order to provide for more adequate aids in tissue engineering.

One group of the more versatile materials developed for tissue engineering are copolymers of a polyalkylene glycol and aromatic esters. These materials have been found to possess highly favorable properties, such as biodegradability and biocompatibility. For these reasons, they are finding increased application in tissue engineering applications, such as in the function of scaffolds for seeding cells of different types. Particularly, copolymers of polyethylene glycol (PEG) and polybutylene terephthalate, which are known under the name of Polyactive™, have been found to give promising results in this regard. In order for the copolymers to be suitable for use in these applications, it is necessary that their shape and morphology can be efficiently controlled.

Previous approaches to provide for porous implants or scaffolds from a variety of materials have included bubble technology, sintering of metals or polymers, expansion of polymer melts and the processing of fibers to felts and meshes.

Another approach is the formation of a porous template after which the porous template is used as a mold for the formation of the desired porous body by filling the pores and interstices of the template with the material from which the porous body is to be constructed, such as a biodegradable thermoplastic polymer. After removal of the template, for instance by dissolving the template material in an appropriate solvent, the porous body can be obtained.

One of the disadvantages of the presently known approaches to porous bodies is that it is difficult to adequately control the various parameters that influence the shape and the morphology of the porous body. For instance, in the template-approach discussed above it is difficult to ensure that all the pores of the porous template have been filled with polymeric material. Another disadvantage of the known techniques is that controlling the pore size and the porosity remains difficult, if at al possible. Furthermore, to allow adequate performance as a scaffold for seeding of cells, it is desirable that the pores of the porous body are interconnected. The present processes lack sufficient controllability in this respect.

Another approach that has been contemplated is to prepolymerize a thermoplastic polymer composition at a temperature above the glass transition temperature of the polymer in a molding step, providing the formed material with a coating of salt particles. The salt particles are subsequently embodied in the thermoplastic material by heating the material to above the melting point. Removal of the salt particles, for instance by a process known in itself in the art as salt-leaching, results in the formation of pores in the thermoplastic material. One of the disadvantages is that a cumbersome two step process is used. Another is that the results are very variable. Hence it remains difficult to manufacture porous structure with interconnected pores in a reproducible fashion while mechanical strength is not compromised.

It is a goal of the present invention to provide for porous bodies that have a reproducible and well-defined pore size and porosity. It is a further goal to come to porous bodies with interconnected pores, preferably homogeneously distributed throughout the porous body. It is another goal to come to implants or scaffolds of biodegradable material that have pores that are better interconnected while at the same time strength of the implant or scaffold is not essentially compromised. Further it is a goal to provide for a more simple an elegant solution to the problem of providing for well defined and reproducible methods for the preparation of porous

bodies that are suitable for use in tissue engineering while at the same time the advantages of the biodegradable material such as Polyactive™ are maintained to a substantial degree.

The present inventors have now found that when particles of a thermoplastic biodegradable polymeric material, a copolymer of polyalkylene glycol terephtalate and an aromatic polyester are mixed with particles that are soluble in a solvent in which the copolymer essentially does not dissolve, and the resulting mixture is subjected to heat and/or pressure a body is formed. When this body is subjected to a step wherein the soluble particles are removed, for instance salt particles being removed by salt-leaching, a porous body remains. It has been found that the thus obtained body combines strength with a high porosity and interconnected pores.

The invention in a first aspect pertains to a method for the preparation of a porous body of a biodegradable material comprising the steps of mixing a copolymer of polyalkylene glycol terephtalate and an aromatic polyester with particles that are soluble in a solvent in which the copolymer essentially does not dissolve, and subjecting the obtained mixture to heat and/or pressure sufficiently long for forming the body.

By mixing a powder of soluble particles and a polymer powder, a homogenous distribution can be achieved. The method provides for an easy and reproducible way of manufacturing porous bodies. Furthermore by varying the amount and/or dimensions of either the polymer powder or the soluble particles, the pore-size, porosity and/or amount of interconnected pores can be controlled in a manner that has not been previously disclosed.

A porous body according to the invention has pores that are interconnected. A qualitative check whether pores are interconnected is by blowing air through the pores. When it is not possible to blow air through the pores, they are not or not sufficiently interconnected. A more quantitative determination of the

porosity can be obtained by mercury porosimetry. The copolymer according to the invention, is a copolymer of a polyalkylene glycol terephtalate and an aromatic polyester. Preferably, the copolymer comprises 20-90 wt.%, more preferably 40-70 wt.% of the polyalkylene glycol terephtalate, and 80-10 wt.%, more preferably 60-30 wt.% of the aromatic polyester. A preferred type of copolymers according to the invention is formed by the group of block copolymers.

The polyalkylene glycol terephtalate may have a weight average molecular weight of about 150 to about 4000. Preferably, the polyalkylene glycol terephtalate has a weight average molecular weight of 200 to 1500. The aromatic polyester preferably has a weight average molecular weight of from 200 to 5000, more preferably from 250 to 4000. The weight average molecular weight of the copolymer preferably lies between 10,000 and 300,000, more preferably between 40,000 and 120,000.

In order to achieve a porous body of sufficient strength, it is important that the copolymer comprises a sufficient amount of the aromatic ester. This means that, if the copolymer contains a relatively high weight percentage of the polyalkylene glycol terephtalate, its weight average molecular weight should be relatively small. If the copolymer contains less of the polyalkylene glycol terephtalate, its weight average molecular weight may be higher. This may be illustrated by the following example. In the case of a copolymer of polyethylene glycol terephtalate and polybutylene terephtalate, it has been found that the copolymer comprises preferably less than 80 wt.% of the polyethylene glycol terephtalate when its weight average molecular weight is 1,000. Based on this information and his ordinary skill, the artisan will be able to select suitable ratios and molecular weights for the polyalkylene glycol terephtalate and the aromatic ester to produce a porous body of sufficient mechanical strength for a certain intended purpose.

The weight average molecular weight may suitably be determined by gel permeation chromatography (GPC). This technique, which is known per se, may for

instance be performed using chloroform as a solvent and polystyrene as external standard. Alternatively, a measure for the weight average molecular weight may be obtained by using viscometry (see NEN-EN-ISO 1628-1). This technique may for instance be performed at 25°C using chloroform as a solvent. Preferably, the intrinsic viscosity of the copolymer lies between 0.2289 and 1.3282 dL/g, which corresponds to a weight average molecular weight between 10,000 and 200,000. Likewise, the more preferred ranges for the weight average molecular weight measured by GPC mentioned above can also be expressed in terms of the intrinsic viscosity.

In a preferred embodiment, the polyalkylene glycol terephtalate component has units of the formula -OLO-CO-Q-CO-, wherein O represents oxygen, C represents carbon, L is a divalent organic radical remaining after removal of terminal hydroxyl groups from a poly(oxyalkylene)glycol, and Q is a divalent organic radical.

Preferred polyalkylene glycol terephtalates are chosen from the group of polyethylene glycol terephtalate, polypropylene glycol terephtalate, and polybutylene glycol terephtalate and copolymers thereof, such as poloxamers. A highly preferred polyalkylene glycol terephtalate is polyethylene glycol terephtalate.

The terms alkylene and polyalkylene generally refer to any isomeric structure, i.e. propylene comprises both 1,2-propylene and 1,3-propylene, butylene comprises 1,2-butylene, 1,3-butylene, 2,3-butylene, 1,2-isobutylene, 1,3-isobutylene and 1,4-isobutylene (tetramethylene) and similarly for higher alkylene homologues. The polyalkylene glycol terephtalate component is preferably terminated with a dicarboxylic acid residue -CO-Q-CO-, if necessary to provide a coupling to the polyester component. Group Q may be an aromatic group having the same definition as R, or may be an aliphatic group such as ethylene, propylene, butylene and the like.

The polyester component preferably has units -O-E-O-CO-R-CO-, wherein O represents oxygen, C represents carbon, E is a substituted or unsubstituted alkylene or oxydialkylene radical having from 2 to 8 carbon atoms, and R is a substituted or unsubstituted divalent aromatic radical.

In a preferred embodiment, the polyester is chosen from the group of polyethylene terephthalate, polypropylene terephthalate, and polybutylene terephthalate. A highly preferred polyester is polybutylene terephthalate.

The preparation of the copolymer will now be explained by way of example for a polyethylene glycol terephtalate/polybutylene terephthalate copolymer. Based on this description, the skilled person will be able to prepare any desired copolymer within the above described class. An alternative manner for preparing polyalkylene glycol terephtalate/polyester copolymers is disclosed in US-A-3,908,201.

A polyethylene glycol terephtalate/polybutylene terephthalate copolymer may be synthesized from a mixture of dimethyl terephthalate, butanediol (in excess), polyethylene glycol, an antioxidant and a catalyst. The mixture is placed in a reaction vessel and heated to about 180°C, and methanol is distilled as transesterification proceeds. During the transesterification, the ester bond with methyl is replaced with an ester bond with butylene and/or the polyethyene glycol. After transesterification, the temperature is raised slowly to about 245°C, and a vacuum (finally less than 0.1 mbar) is achieved. The excess butanediol is distilled off and a prepolymer of butanediol terephthalate condenses with the polyethylene glycol to form a polyethylene/polybutylene terephthalate copolymer. A terephthalate moiety connects the polyethylene glycol units to the polybutylene terephthalate units of the copolymer and thus such a copolymer also is sometimes referred to as a polyethylene glycol terephthalate/polybutylene terephthalate copolymer (PEGT/PBT copolymer).

The copolymer used in the present invention is preferably in a particulate form such as a granulate or a powder. The polymeric material can be manufactured in particulate form by various technical means such as milling, granulating and other means. One preferred method of providing for the polymeric material in particulate form is milling at low temperatures. To this end granules of the polymeric material are cooled, for instance by liquid nitrogen and crunched to a powder. The desired fraction can be obtained by sieving the powder. The sieve mesh is typically 500 μm or

less, and may be adjusted to obtain particles of the desired size in any manner known by the skilled professional. The sieve fractions of the polymeric particles according to the invention range from particles with diameters in the range from 10-1000 μm, preferably from 20-500 μm, more preferably from 50-250 μm. Very good results have been obtained with a sieve fraction obtained using a mesh in the range of about 75-125 μm, e.g. about 100 μm. When the polymeric particles are too large, the homogeneity of the resulting body can be compromised, leading to a body that is insufficiently homogeneously porous and of which the mechanical strength may become too low. When the particle size is too low, a relative strong porous body is obtained, however, the pores in the porous body may have a low fraction of interconnected pores.

The particular material that is used as the removable component in the present invention is solid and should be soluble in a non-toxic solvent in which the copolymer essentially does not dissolve, e.g. water. , This means that the particular material should be easily and essentially completely removable by rinsing or soaking or the like with said solvent. During said rinsing or soaking, the copolymer should essentially not be removed or affected. The soluble particle material is preferably free of crystal water and is preferably of a material that is generally regarded as non-toxic with respect to the intended use (tissue engineering). The particle material should be relatively thermostable, particularly if the preparation of the porous body comprises a heating step before the soluble particles are removed. A particle may comprise one or more chemical substances, i.e. mixtures and the like can also be used. Examples of suitable soluble particular materials include salts, (poly)saccharides (e.g. starch, saccharose), and polymers, such as poly(meth)acrylates (e.g. poly(methyl metharcrylate)).

In a preferred embodiment the soluble particular material is a salt. Preferred salts are NaCl, KCl, sodium citrate, $CaCl_2$ and similar salts that are non-toxic, well soluble in the solvent (e.g. water) and preferably relatively low priced. The

soluble particles are preferably substantially free of heavy metals, because of the toxicity of such metals. Incorporating water soluble salts in the polymer material allows for a simple process such as salt-leaching to remove the salt from the formed body, leaving a porous body behind that is suitable in tissue engineering as a medical implant or a scaffold. The soluble particular material preferably has a particle size in the same range as mentioned above for the copolymer. Accordingly, the particles may have been obtained using a sieve mesh obtaining particles with diameters in the range from 10-1000 μm, preferably from 20-500 μm, more preferably from 50-250 μm. Very good results have been obtained with a sieve fraction obtained using a mesh in the range of about 75-125 μm, e.g. about 100 μm.

The amount in which the soluble particular material is used, will depend on the desired degree of porosity of the porous body and on the manner in which the body is to be formed. In case pressure is applied, the amount preferably corresponds to at least the bulk density of the solid particular material under the circumstances. When sodium chloride is used, this means that at least 63 % (v/v) with respect to the copolymer is used. In a preferred embodiment, the amount of soluble particular material used is at least 75 % (v/v), with respect to the copolymer. The upper limit of the amount of the soluble particular material is preferably 85 % (v/v), more preferably 80 % (v/v), with respect to the copolymer. The required amount of the soluble particular material to obtain a certain interconnected porosity will in general be in an inverse relationship to the average particle size of said particles.

To the mixture of soluble particles and copolymer a plasticizer can be added to improve the processability of the mixture. The plasticizer can be incorporated in the powdered polymeric material at any given point, prior to the application of heat and/or pressure. The plasticizer should be soluble in a solvent wherein the polymer is essentially not soluble. Preferably the plasticizer is soluble in the same solvent as the soluble particles. Further, the plasticizer should preferably

be non-toxic. A preferred plasticizer is NMP, N-methylpyrrolidone. Other additives can be used in a similar fashion

The mixture of soluble particles and copolymer and optional additives is subjected to heat and/or pressure. Suitable methods for the application of heat and/or pressure are for instance molding, preferably injection molding, pressing such as plate pressing or plunger pressing, but also sintering is an applicable method and considered to fall within the scope of the invention. When sintering is used, the amount of soluble particular material used is preferably below the bulk density of said material under the conditions employed. Very good results have been achieved with a method wherein plates of the mixture of copolymer and soluble particles of a size of 20x20 cm was subjected to a pressure of 12.5 - 50 pounds/cm^2 at a temperature of approximately 220 °C for a duration of 5-10 min. The skilled professional will know how to optimize the duration depending upon the thickness of the plates, the temperature conductivity, and other parameters of the mixture. It is important that the combination of temperature and duration is such that all the polymer is melted .

In order to obtain the porous body, it is preferred that after subjecting the body to heat and/or pressure, the soluble particles are removed. One highly suitable way of doing this, is by submerging the body with the soluble particles in demineralized water or another suitable, non-toxic solvent in which the copolymer essentially does not dissolve, to allow the particles to dissolve. It is preferred to treat the water with UV prior to using it for dissolving the particles. Generally, it will be desired to repeat this procedure in demineralized water to achieve a substantially complete removal of the soluble particles. Once the soluble particles have been removed to a sufficient extent, the body may be dried, preferably slowly and under ambient conditions. The material may further be processed, e.g. by cutting, punching, drilling, grinding, chopping etc.

The invention in another aspect pertains to a porous body that has been obtained by the method according to the invention.

The invention also pertains to a medical implant or a scaffold that comprises a porous body. The scaffold or medical implant defines the construct shape and dimensions of the replacement to be implanted. Generally, it is manufactured of a porous biodegradable material according to the invention, so that the degradation of the scaffold proceeds parallel with accumulation of tissue components (growth and synthesis of extracellular matrix (ECM)). Thus, the function of the scaffold, the provision of shape and strength, will gradually be taken over by the formed tissue components. One example of a medical implant which may be manufactured of the present porous body is a plug that may be inserted at the site of harvesting of autologous bone tissue (e.g. in the iliac crest) for pain relief.

The invention will now be elucidated by the following, non-restrictive examples.

Example 1

In a beaker, 30 g copolymer of polyethylene glycol (PEG, MW = 1000 g/mole) and polybutylene terephthalate (PBT), wherein the weight percentage PBT was 30 w/w%, and 162.4 g Sodium Chloride (NaCl) was mixed manually. The particle size of the copolymer was in the range of 50-250 μm and the particle size of the NaCl was 500-600 μm.

A mould with outer dimensions of 20 x 20 x 1 cm and inner dimensions of 8 x 12 x 1 cm was filled with the mixture. The mould was closed and transferred to a plate press with plates of 20 by 20 cm, heating till 300°C and "crash" cooling. The mould was pressed at 15,000 pound and 220°C for 10 min. Hereafter the mould was cooled down till room temperature. After opening the mould and removing the block out of the mould the block with salt was transferred into a glass beaker filled with demineralised water to dissolve the salt particles.

The demineralised water was refreshed every 4-16 hour for at least 4 times. The conductivity of the water was measured. When the conductivity of the

water was more than 25 μS after more than 4 hours of extracting the water was refreshed again. When the conductivity was less than 25 μS the block was removed out of the water. The block was dried under ambient conditions and subsequently dried in a vacuum oven at 25°C.

After drying the block was visually inspected on colour, cracks, inhomogeneity and black spots. The porosity and interpore connection of the scaffold was checked by mercury porosimetry (Thermo Finnigan Pascal 140).

Results showed that 90 % of the pores could be reached by interpore connections with a diameter of 100 μm or higher.

With this method a strong 77 v/v% porous interconnected block could be made. No cracks, inhomogeneity and black spots were determined. The colour was off-white. The block was easy to shape by e.g. a scalpel knife or a pair of scissors.

Example 2

In a beaker, a 1 kg mixture containing 25 v/v% of a copolymer of polyethylene glycol (PEG, Mw 300 or 1000 g/mol) and polybutylene terephthalate (PBT), wherein the weight percentage PBT was 55 or 70 w/w%, and 75 v/v% sodium chloride (NaCl) was made.

After drying the mixture was transferred into the hopper of a Battenfeld 150-050 CD injection moulding machine. A mould with inner dimensions of 7 cm in diameter and 2 cm height was installed in the injection moulding machine. The temperature settings were 190°C for all heating zones. The cycle time was 30 seconds.

After injection moulding the block was put into a glass beaker filled with demineralised water to dissolve the salt particles. The leaching and drying process were performed as described in example 1.

After drying the block was visually inspected on colour, cracks, inhomogeneity and black spots. The porosity was determined by measuring the dimensions and the weight of the block. The porosity was calculated with formula 1.

$$porosity = 1 - \frac{weight(grams)}{length(cm) \times width(cm) \times thickness(cm) \times \rho} \qquad (1)$$

The densities (ρ) of the different copolymer composition can be found in table 1.

Table 1: density of different PEG/PBT copolymer compositions.

MW PEG	wt% PEG	ρ (g/cc)
300	55	1.25
1000	70	1.20

With this method a strong 75 v/v% porous block could be made. No cracks, inhomogeneity and black spots were determined. The colour was off-white. SEM pictures showed square pores with a main pore size of 500-600 μm. Also some smaller pores and interpore connections are noticed. The block was easy to shape by e.g. a scalpel knife or a pair of scissors.

Example 3

Porous blocks (8 x 12 x 1 cm) were prepared as described in example 1. Instead of Sodium Cloride (NaCl), Sodium Citrate ($C_6H_5Na_3 \cdot 2H_2O$) with a particle size of 500-1000 μm was used. Before processing the Sodium Citrate the hydrated water was dehydrated in a vacuum oven at 200°C for at least 24 hours.

With this method strong 77 v/v% porous blocks could be made. No cracks, inhomogeneity and black spots were determined. The colour was off-white. SEM pictures showed round pores with a main pore size of 500-1000 μm. Also some smaller pores and interpore connections were noticed. The block was easy to shape by e.g. a scalpel knife or a pair of scissors.

Claims

1. Method for the preparation of a porous body of a biodegradable material comprising the steps of mixing a copolymer of polyalkylene glycol terephtalate and an aromatic polyester with particles that are soluble in a solvent in which the copolymer essentially does not dissolve, and subjecting the obtained mixture to heat and/or pressure sufficiently long for forming the body.

2. Method according to claim 1, further comprising a step wherein the soluble particles are removed from the body.

3. Method according to claim 2, wherein the soluble particles are removed by dissolving.

4. Method according to any one of the claim 1-3, wherein the soluble particles comprise a salt, a (poly)saccharide, and/or a polymer.

5. Method according to claim 4 wherein the salt is NaCl, KCl, sodium citrate, $CaCl_2$, or a mixture thereof.

6. Method according to claim 4 wherein the (poly)saccharide is starch, saccharose or a mixture thereof.

7. Method according to claim 4, wherein the polymer is poly(methyl methacrylate).

8. Method according to any one of the claims 1-7, wherein the soluble particles have dimensions in the range of 10-1000 μm, preferably 20-500 μm, more preferably 50-250 μm.

9. Method according to any one of the claims 1-8, wherein the copolymer has the form of particles having dimensions in the range of 10-1000 μm, preferably 20-500 μm, more preferably 50-250 μm.

10. Method according to any one of the claims 1-9, wherein the soluble particles are used in a relative amount of at least 63 % (v/v), preferably at least 75 % (v/v), with respect to the copolymer.

11. Method according to any one of the claims 1-10, wherein after removal of the soluble particlesthe body contains interconnected pores.

12. Method according to any one of the claims 1-11, wherein further a plasticizer is mixed with the salt and copolymer particles.

13. Porous body obtainable by the method of any of claims 2-12.

14. Medical implant or scaffold comprising porous body as defined in claim 13.

15. Medical implant or scaffold according to claim 14, further comprising biological material.

16. Use of a porous body as defined in claim 15 in tissue engineering or as a medical implant.

INTERNATIONAL SEARCH REPORT

PCT/NL 02/00066

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L27/44 A61L27/48 A61L27/56 A61L27/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C09J C08J C08L B29C A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 6 103 255 A (LHOMMEAU CHRISTELLE M ET AL) 15 August 2000 (2000-08-15) abstract column 3 -column 5 column 6, line 59-67 column 9, line 4-44 ---	1-6,8,9, 11,13-16 1-6, 8-11, 13-16
Y	WO 99 32204 A (UNIV TEXAS) 1 July 1999 (1999-07-01) abstract page 22 -page 26 page 33 -page 35 --- -/--	1-6, 8-11, 13-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 March 2002	19/03/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Böhm, I

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 002 859 A (ISOTIS B V) 24 May 2000 (2000-05-24) abstract column 2 -column 4	1-6,11, 13-16
A	US 4 076 656 A (WHITE LEROY A ET AL) 28 February 1978 (1978-02-28) abstract column 3 -column 4	1-6,8, 11-16
A	EP 1 068 872 A (ISOTIS B V) 17 January 2001 (2001-01-17) abstract	1

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/NL 02/00066

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